19. (amended) The method of claim 17 wherein the [epitope] peptide binds to the autoantibodies to block the autoimmune response.

20. (amended) The method of claim 17 wherein the [epitopes] peptides are administered in combination to block an autoimmune response involving more than one autoantibody.

Remarks

Insertion of Trademark ™

As requested, ™ has been inserted into the specification where appropriate.

Amendment of Title

The title has been amended to reflect that the claimed reagents are peptides.

Election of Species

Applicants affirm again their election of species. It is understood, however, that the restriction requirement has been withdrawn and that all claims are therefore pending until a final determination that no generic claim is allowable.

Obviousness Type Double Patenting

An appropriate Terminal Disclaimer with U.S.S.N. 07/648,205 will be submitted when there are allowable claims in the present application.

Rejections under 35 U.S.C. §112

Claims 1-3 and 7-20 were rejected under 35 U.S.C. §112 as indefinite on the basis that it is unclear whether applicants are claiming peptides or epitopes. This rejection is respectfully traversed if applied to the amended claims.

Applicants are claiming peptides that form epitopes having the claimed sequence. This is inherent in the language in claim 1 "linear epitope" (as opposed to "conformational epitope", where the epitope can be formed by the three dimensional structure of a protein, rather than by contiguous amino acid sequence).

The claims have been amended to use the term "peptides" in claims 1-11, 12, and 17, rather than epitopes, which could be confusing. This should also obviate the rejection as to claim 2.

Claim 16 refers to prognosis, not diagnosis, because this is used to predict the course of the disease, rather than to define the cause or nature of the disease.

Rejection under 35 U.S.C. §101

Claims 1-3 and 7-20 were rejected under 35 U.S.C. §101 on the basis that applicants have not conclusively demonstrated the specificity of the peptide reaction with autoantibodies (utility in diagnosis) or *in vivo* utility as a therapeutic or vaccine.

The Examiner's attention is drawn to applicant's co-pending application U.S.S.N. 08/160,604 filed November 30, 1993,

which describes the use of these peptides to make animal models of autoimmune disorders. It is well established that the same antigens used to induce protective immunity can also be used to induce tolerance (the classic "allergy shots"). Accordingly, there is no reason to predict that applicants' claimed peptides, demonstrated to be useful to raise a disease specific response, will not be useful in inducing tolerance.

More to the point, the data in Table 2 shows that the peptides react with very high specificity to naturally occurring autoantibodies. See also page 12, last paragraph, and page 24, describing the reactions with specific patient sera. The following data relating to substitutions and modifications in the peptides and their effects on binding data provides even more support for specificity.

The Examiner's remarks on page 5, lines 13-18, are not understood. Applicant would be happy to discuss this issue with the Examiner if this would be helpful. Normal sera does not contain autoantibodies to the claimed peptides. Autoantibodies, not peptides, cause disease. There is background absorbance in the assay, which is why normal sera is used as a negative control. As noted in the footnote to Table 1, epitopes are termed reactive if binding is at least **three and one-half times as great** above background.

Rejections under 35 U.S.C. §112

The specification has been objected to and claims 1-3 and 7-20 rejected under 35 U.S.C. §112, second paragraph, on the basis of non-enablement. These rejections are respectfully traversed.

Diagnositic use.

All of the examples demonstrate binding of the claimed peptides to autoantibodies. This is the basis of the test used to determine the reactive epitopes. Methods have been clinically available for many years to screen patient sera for antibodies where the antigen is known. This is routine laboratory work. Antigen can be added to agar in immunodiffusion plates in the simplest and oldest form of checking for the presence of autoantibodies, radiolabelled and used in a more sophisticated binding assay, or utilized in an Elisa as described in the examples, which provide the exact reaction amounts and conditions.

In summary, the application very clearly describes how to use the peptides for diagnostic purposes, i.e., to screen patients for the presence of specific autoantibodies.

Therapeutic applications.

Again, the Examiner's attention is drawn to the examples, all of which use patient sera. The results are shown to be statistically significant (i.e., binding to reactive peptides is defined as at least three and one-half times greater

than to normal sera). With respect to the methods described at pages 8-10, more detail is not required for **one of ordinary skill in the art**. It is well established what kinds of doses of antigen are required to induce tolerance; or at worse, the doses required to determine the optimal amounts required to induce tolerance, since there is frequently individual variation. However, applicants have not invented a methodology for inducing tolerance; only the means to do so.

There is no undue experimentation

What are claimed are peptides of up to forty amino acids including the claimed linear amino acid sequences which have been experimentally determined to bind to autoantibodies from patients. Peptides do not "recognize antibodies". Antibodies have a variable region which binds to a short amino acid sequence. Applicants have listed those exact amino acid sequences which were experimentally determined to react with autoantibodies. Please note the use of the term "autoantibodies", based on a pool of antisera obtained from patients having a particular diagnosed disorder. This is not a single antibody. Accordingly, there is no undue experimentation. All of the claimed peptides were shown experimentally to bind to autoantibodies in a statistically significant manner. Applicants' small, non-profit research laboratory screened over 7000 peptides to determine those which bound. They synthetically

created each of the peptides by making octapeptides based on the known sequences for each of the autoantigens, by taking amino acids 1-8, then 2-9, then 3-10, then 4-11, then 5-12, etc. until they tested each one for binding. This was done for each of the claimed antigens. As the Examiner has correctly noted, not all of the possible peptides derived in this manner did bind in a useful manner; as noted above, over 7000 peptides were screened.

The Examiner's statement at page 8, lines 19-21, is simply not understood. As discussed above, the epitope consisting of several amino acids is bound by autoantibodies; peptides do not recognize epitopes. With respect to the question of tertiary structure, the claimed epitope is defined as a **linear** epitope - this requires the use of the contigous amino acid sequences.

Applicants would appreciate the Examiner pointing to where in the specification he finds support for the statements in paragraph c on page 9 of the Office Action - or perhaps states his concern in a different way. The sera contains the autoantibodies that are reactive with the peptides. The more autoantibodies (higher titer) of more types (i.e., anti-Ro, anti-La/SSB, etc), the more likely the disease is severe. This is routine for doctors treating patients having autoimmune disorders (such as applicants, who see many patients each day, and diagnose

their condition and prognosis based on the results obtained using less specific diagnostic tests).

Claims 1, 12, and 17 have been amended to add the other peptides described in the application at page 19, line 21, to page 20, line 10. Although there was an election of species, these are also exemplary species which fall within the generic scope of claims 1, 12, and 17.

Rejections under 35 U.S.C. §103

Claims 1-3, 8, 10-17, 19, and 20 were rejected under 35 U.S.C. §103 as obvious over Deutscher, et al., Proc. Natl. Acad. Sci. 85:9479-9483 (1988) in view of U.S. patent No. 4,784,942 to Harley, Dryberg, et al., Current Topics in Microbiol. 130:25-37 (1986), Geysen, et al., J. Immunol. Methods 102:259-274 (1987), and Voller, et al. Manual Clin. Lab. Immunol. Ch. 17 (1986). Claims 1-3, and 7-20 have also been rejected under §103 as obvious over Deutscher, et al., in combination with Harley, U.S. patent No. 4,554,101 to Hopp, and Voller, et al. These rejections are respectfully traversed.

Deutscher, et al.

Deutscher, et al., discloses the amino acid sequence of the human 60 kDa ribonucleoprotein. They state that the protein is useful in assays. Stating that an infectious disease may play a role in an autoimmune disorder, even in combination with the amino acid sequence of one autoantigen, is a far cry from saying

that one should screen every overlapping octapeptide formed by the sequence as claimed.

There is no basis applicants can find for the Examiner's assertion that "It would have been obvious . . . that in view that infectious agents are implicated in the etiology of autoimmune diseases . . . that antibodies to the 60 kD protein would be useful in the prevention of autoimmune disease associated with 60 kDa protein". Moreover, not only is this **not** what applicants are claiming, there appears to be no relevance to this statement to what they are claiming.

Harley

Harley does not teach the use of immunogenic fragments to reduce unwanted sample interactions; Harley teaches the use of **antibody** ("immunoglobulin") fragments to reduce background.

Dryberg, et al.

Dryberg, et al., states that homology between antigenic determinants shared by infectious agents and host proteins could cause an autoimmune response.

Other publications make similar statements relating to cancer and many other disorders.

These constitute speculation; not proof of concept nor much less an enabling disclosure. Dryberg, et al., state that one can compare "homology" (whatever that means) of antigenic determinants to determine what the common features are.

Applicants have chosen a totally different means to determine useful antigenic epitopes: construction of overlapping, contiguous peptides that are reacted on solid phase with autoantibodies. These are linear epitopes, not three dimensional epitopes. There is no "homology"; either the sequence is bound, or it is not bound to a significant degree.

Geysen, et al.

Geysen, et al., discloses a method similar to that used by applicants to define epitopes. There is no disclosure, however, of how to determine which of the epitopes bind to a significant degree; which would be useful in diagnostic or therapeutic methods; nor how to use the peptides that meet the foregoing criteria.

Voller, et al.

Voller does disclose standard antibody-antigen assays that could be adapted for use with applicants' claimed peptides, given the peptides.

Hopp

Hopp discloses a method for making immunoglobulins which are specific for a region of an antigen where there is the greatest local average **hydrophobicity** (not hydrophilicity) (last line of abstract).

The relevance of a method for defining a potential epitope based on hydrophobicity of the amino acids (table at top

of col. 2) is unclear. Applicants are claiming peptides determined on the basis of their reactivity with antibody. Hydrophobicity of the various amino acids is never used.

It is agreed that Hopp supports applicants' statements that those of ordinary skill in the art would know how to use the claimed peptides, *once they had been identified*.

The combination of the art

As discussed above, Dryberg, et al., has no relevance since he is looking at three dimensional structure and stating that homology may be useful in determining epitopes; he is not looking at binding of specific overlapping sequences. Hopp is just as irrelevant since applicants do not use hydrophobicity to determine their claimed peptides, nor would one derive the same peptides if one did so.

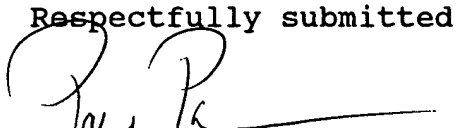
Voller, et al., is relevant only as to the utility of applicants' claimed peptides since there is nothing about determining useful peptides. Harley is no more relevant since he simply states that antibody fragments can be used to decrease background.

It is clear that there is no teaching among the remaining cited art as a whole that would lead one to applicants' claimed peptides. This would require that one of ordinary skill in the art pick parts of Geysen's method, combine with parts of the sequence of Deutscher, et al., and then reasonably predict

which out of all the possible sequences that could be tested, which peptides would be useful. This is patently absurd. If this were so obvious, applicants would not limit their claims to specific peptides, but would try to claim the generic group (i.e., antigenic peptide fragments of autoantigens). As noted above, many of the peptides tested by applicants did **not** work - there was simply no reliable way to predict which would, and which would not, be useful. Accordingly, the claimed peptides, and methods for use thereof, cannot be obvious from the cite art nor any other prior art.

Allowance of all claims 1-20, as amended, is earnestly solicited.

Respectfully submitted,



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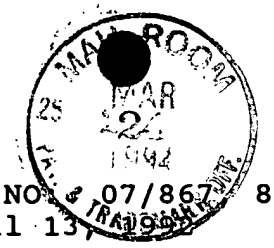

U.S. SERIAL NO. 07/867,819
FILED: April 13, 1992
AMENDMENT

CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date: March 21, 1994

Patrea Pabst